

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220**FOR FURTHER ACTION**
See paragraph 2 belowInternational application No.
PCT/GB2005/000341International filing date (day/month/year)
01.02.2005Priority date (day/month/year)
03.02.2004International Patent Classification (IPC) or both national classification and IPC
C07D239/42, C07D405/12, A61K31/506, A61P37/04, A61P29/00, A61P19/02, A61P19/10Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/GB2005/000341**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial
applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 9, 10

because:

☒ the said international application, or the said claims Nos. 9, 10 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-10
Inventive step (IS)	Yes: Claims	
	No: Claims	1-10
Industrial applicability (IA)	Yes: Claims	1-8
	No: Claims	

2. Citations and explanations**see separate sheet**

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)**and / or****2. Non-written disclosures (Rules 43bis.1 and 70.9)****see form 210**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/GB2005/000341**Re Item III****Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 9 and 10 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1** Reference is made to the following documents:

- D1: WO 02/04429 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; THOMAS, ANDREW, PETER; NEWCOMB) 17 January 2002
- D2: EP-A-0 569 912 (HOECHST AKTIENGESELLSCHAFT) 18 November 1993
- D3: SULLIVAN R.W., BIGAM C.G., ERDMAN P.E., PALANKI M.S.S., ANDERSON D.W. ET AL: "2-chloro-4-(trifluoromethyl)pyrimidine-5-N-(3',5'-bis(trifluoromethyl)phenyl)carboxamide" J. MEDICINAL CHEM., vol. 41, no. 4, 1998, pages 413-419, XP002328712
- D4: WO 97/09315 A (SIGNAL PHARMACEUTICALS, INC; SUTO, MARK, J; GOLDMAN, MARK, E; GAYO, LE) 13 March 1997
- D5: WO 02/066036 A (BRISTOL-MYERS SQUIBB COMPANY) 29 August 2002

2. Novelty. Article 33(2) PCT:

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

Document D1 discloses in method 75 p.71, methods 120 and 121 p.77, three specific compounds that fall within the scope of current claim 1.

Dependent claims 2-10 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty (Article 33(2) PCT).

The compounds of D2-D4 are explicitly excluded from the scope of claim 1 by a proviso

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concerning R6. The generic formula of compounds in Claim 1 of D5 encompasses the subject-matter of present claim 1. Since this document does not contain specific examples of compounds claimed in the present application, D5 is not considered to be novelty destroying.

3. Inventive step, Article 33(3) PCT:

The present application is related to trisubstituted pyrimidine compounds of formula (I) that are able to modulate the cannabinoid 2 receptors (CB2); these compounds are useful in the treatment of immune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis or osteoporosis.

Document D4 discloses structurally similar compounds, useful for the treatment of the same diseases, namely for the treatment of autoimmune or immun-inflammatory diseases such as rheumatoid arthritis or multiple sclerosis (see claims 37-42 in D4). It appears to be irrelevant that D4 does not disclose specifically the CB2 receptor affinity since it refers to the same use in terms of disorders to be treated. In fact, it should be borne in mind that the selective occupation of a receptor cannot be considered in itself as a therapeutic application; the discovery that a substance selectively binds a receptor, even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a defined, real treatment of a pathological condition in order to make a technical contribution to the art and to be considered as an invention eligible for patent protection.

Thus, D4 should be equally considered as the closest prior art.

The compounds of D4 differ from those claimed only on account of the disclaimer in current claim 1.

The structural difference between the compounds of D4 and those presently claimed is to be regarded rather as a minimal structural difference so that it is considered that the technical problem of providing further CB2 ligands has been solved in an obvious way, since the retention of biological activity of the present compounds was to be expected in the light of D4.

Hence the problem underlying the present application has to be seen the provision of CB2 modulators that present an unexpected effect with regard to the compounds of D4. There is no evidence in the present application for such surprising effect compared to the compounds of D4. In the absence of evidence of such advantages, Article 33(3) PCT cannot be

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considered to be satisfied.

4. Industrial applicability:

For the assessment of the present claims 9 and 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI**Certain documents cited**

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO2004/029027	08.04.2004	25.09.2003	27.09.2002
WO2004/029026	08.04.2004	25.09.2003	27.09.2002
WO2004/018434	04.03.2004	19.08.2003	21.09.2002
WO2004/018433	04.03.2004	19.08.2003	21.09.2002

These documents are all related to CB2 modulators.